Identification of a geographic area characterized by extreme longevity in the Sardinia island

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Age-validation and non-random Spatial Distribution of Extreme Longevity in Sardinia : the AKEA Study.

Age-validation is not developed in this paper. What about the following proposal : "Identification of a non-random Spatial Distribution of Extreme Longevity in Sardinia : the AKEA Study »

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Introduction

Extreme longevity in humans has attracted a great interest in the last decade. However, the prevalence and the distribution of very old people (including centenarians) in specific geographic areas has not been sistematically studied, in order to ascertain possible differences and/or commonalities. In Italy we recently performed an epidemiological representative study on all centenarians living in Sardinia (AKEA study) (Deiana et al. 1999). The most remarkable finding of this investigation were the following: i. a prevalence of centenarians higher than in other European countries (16.6 over 100.000 inhabitants) *Table 1 will show that the global figure for prevalence is not higher compared to Central Italy*, and ii. *a lower* female/male ratio of 2 to 1 (Deiana et al., 1999). Both these phenomena were particularly evident in the Nuoro province, the most remote and mountainous among the four Sardinian provinces. These findings were remarkable since all previous reports on exceptional long living populations concentrated in specific geographical area have later been invalidated and explained by age misreporting or other errors in data collection (Jeune and Vaupel, 1995, 1999). Moreover Sardinia is particularly interesting owing to peculiar characterstics of the island from a demographic, historical and cultural point of view. Indeed, Sardinians remained genetically isolated for a number of centuries and experienced no immigration in its recent history. Living habits has remained almost constant over the years particularly in some parts of the island where strong cultural and anthropological traditions are still present.

The major aims of the present study were the following:

1. To validate, from a demographic point of view, the above mentioned data about the high prevalence of centenarians and particularly of male centenarians;

2. to test the hypothesis that a geographic area exists in the central part of Sardinia whose population is characterized by an exceptional high longevity, and that the geographical **distribution of centenarians** in Sardinia is non-random;
3. to compare the data obtained as a results of this investigation in Sardinia with available data on other European or extra-European specific geographic areas.

Material and Methods

Age validation of the data on Sardinian centenarians.

To validate the age of the centenarians identified in the AKEA study (Deiana et al., 1999) we used multiple and independent new data sources. In particular, we personally visited the Registry Office of 40 municipalities, mainly located in the Nuoro and Sassari provinces, and choosen on the basis of their highest prevalence of centenarians and the presence of the oldest male centenarians. In each of these Registry Office we carefully checked the original *birth records* and collected additional data using different data sources (population register, marriage register, death register…). Date of birth, date of marriage and date of death of the centenarians, as well as other demographic data including information *on parents, siblings and children* were recorded. Such an approach allowed us to perform a cross-matching of the demographic data and to assess their self-consistency and non contradiction for each centenarian. *As a matter of fact extreme age observed in Sardinia have been validated and this result is bringing a lot of interest on possible explanations for this exceptional longevity especially for men (I suggest to introduce here a note on Antonio Todde, Giovanni Frau and Damiana Sette plus reference to Montpellier paper).*

Identification of the Sardinian geographic area with the highest prevalence of centenarians by the extreme longevity index (ELI)

The most simple way to identify the geographic area with the highest prevalence of centenarians would be to group all municipalities with the highest prevalence of the centenarians identified during the AKEA study. However, such a simple approach cannot be used as the crude prevalence of centenarians, *the number of living centenarians reported to total resident population,* is potentially misleading because it can be largely influenced by migrations and changes in the structure of the population over a century. ~~*Moreover, the administrative boundaries of municipalities often do not identify territories that are different either geographical or culturally.*~~ In order to overcome these difficulties we first calculated the **extreme longevity index** (ELI) defined as the proportion of all persons who became centenarians among those who were born in Sardinia in a given period ~~of twenty years~~, i.e. between 1880 and 1900.

This index, used in historical demography, is substantially more accurate and reliable than the simple prevalence ~~measured for a single defined year,~~ because the number of centenarians that can be used in the calculation is much higher. Assuming that some members of the 1880-1900 cohorts emigrated outside Sardinia, became centenarians but could not be identified , the ELI reconstructed from historical data may therefore be slightly underestimated. In any case, as we are only considering centenarians born in Sardinia, ~~the immigration rate was minimal over the last century,~~ overestimation of ELI is impossible.

In order to calculate ELI over all the Sardinian municipalities (n. 377), the data on centenarians who died in the year 1980 to 2000[i] provided by the Italian National Statistical Institute (ISTAT) ~~for the year~~ was combined with the estimated number of births in these municipalities for the years 1880-1900[ii]. Such a procedure was performed under the preliminary hypothesis of zero net migration within Sardinia for centenarians. In other words, in this first step, it was assumed that centenarians lived and died where they were born and based on this assumption a first estimation of ELI is calculated for all Sardinian municipalities.

The geographical distribution of Sardinian centenarians and the use of a multiscalar smoothing method to assess their spatial aggregation

A further analysis was aimed at testing the hypothesis that the geographical distribution of centenarians in Sardinia is non-random and that a peculiar geographical area, where the estimated value of ELI is consistently and significantly higher than the average value observed in the whole Sardinia, could be identified. In order to identify such a geographic area a spatial deterministic model was used. In such a way we tested the hypothesis that areas with high ELI and areas with low ELI are organized in clusters whose members are spatially adjacent (i.e. positive spatial autocorrelation). Thus, we selected all municipalities with an ELI value higher than the average for the whole Sardinia, excluding municipalities with high ELI values but completely surrounded by municipalities with low ELI values, and including municipalities with low ELI values but completely surrounded by municipalities with high ELI values. In this way 214 municipalities were identified and ~~personally~~ visited to check the place of birth of all centenarians (living or dead in each municipality) born between 1880 and 1900[iii]. In particular, for each municipality, the number of centenarians born in the municipality (X) and the total number of newborns for the same cohorts (P), i.e. the population “at risk” to become centenarian, were considered, and a new value of ELI was calculated without hypothesis of zero net migration.

Thereafter the difference between the number of centenarians observed in commune i, X(i), and the expected theoretical number of centenarians for the same commune X*(i) based on the number of births P(i) and the average ELI for the whole Sardinian population ($X_{tot}/P_{tot} = 1132/516276 = 0.00219$) was calculated according to:

$$X^*_i = P_i \,.\, (X_{tot}/P_{tot}) = P_i * 0.00219 \qquad (1)$$

The criteria used to identify positive difference between a specific commune and the whole Sardinia was the chi-square distance between theoretical and observed numbers of centenarians as follows :

$$Chi2(i) = [X^*_i - X_i]^2 / X^*_i \qquad (2)$$

Therefore the significance of each difference has been tested through a chi-2 table with one degree of freedom if the theoretical number of centenarians was large enough, **i.e. equal or higher to 5% probability of significant deviance**. *Considering the average probability of centenarians per births, it was possble to calculate the requested minimal number of births per basic area, in order to find significant results. To attain this minimum required number, a spatial aggregation method was used.* In particular, a multiscalar potential smoothing method based on gaussian neighbourhood (Grasland, Mathian, Vincent, 2000) was considered an optimal solution, as it allowed a continuous measurement of the phenomenon, without considering the discrete aspect related to the administrative division of the Sardinian territory (377 municipalities).

Sardinia demographic data

The Demographic data for the Sardinia island (population number, mortality rates....) are from ISTAT.......

What kind of data has to be presented here for Sardinia ?

RESULTS AND DISCUSSION

Age validation.

On the whole, the entire validation procedure led us to visit and to check data regarding 40 municipalities (see appendix 1 for details : What is the proposed contain for Annex 1 ?). All the data regarding **XY** centenarians previously identified and described in the AKEA study (Deiana et al., 1999) were confirmed. Only one mistake was found, as a female centenarian who, according to the Death Registry of Villagrande municipality died in 1997 at 110, was in fact her younger sister born three years later as the first one died at 22 months. Thus her age at death was 107 instead of 110. These results definitely confirm the high prevalence of centenarians in Sardinia and the very low ratio between female and male centenarians in the island (2:1) and particularly in the Nuoro province (1:1) previously reported (Deiana et al., 1999). We think that age validation of the oldest olds is an important prerequisite and a starting point for developing interdisciplinary investigations aimed to identify the determinants of extreme longevity in humans on biological and genetic determinants of longevity

Geographical mapping of Sardinian centenarians: the Extreme Longevity Index

The results of AKEA study (Deiana et al., 1999) and of the here reported age-validation open the question of the possible components and determinants of such a remarkable demographic phenomena. To clarify this point we first tried to answer the question whether the geographic distribution of centenarians in the island was uniform or showed some type of aggregation and clustering. Thus, we took advantage of an index which has been utilized by historical demographers for other purposes, i.e. the Extreme Longevity Index (ELI). Dividing the number of centenarians by the number of births gives the value of ELI as the probability to become centenarian (ELI = X/P, where X is the number of centenarians born in each municipality and P is the total number of newborns).

However, we introduced a first important improvement. To obtain reliable results over a relatively long time period regarding a very high number of centenarians we considered the data of 21 consecutive birth cohorts of the entire Sardinia for the years 1880-1900. Accordingly, for the whole Sardinian population the average value of ELI was 0.00**219** calculated as follows: 1132 centenarians among birth cohorts 1880 - 1900 divided by the total size of the birth cohorts, i.e. 516.276 new-borns.

Identification of geographical areas with different longevity: the Blue Zone

Using this index along with an adequate spatial analysis we identified a geographic area with high levels of extreme longevity. Indeed, the results of the ELI analysis applied to the entire Sardinia island, taking into account the sum of contiguous communes as described in Materials and Methods (exclusion of municipalities with high ELI values but completely surrounded by municipalities with low ELI values, and inclusion of municipalities with low ELI values but completely surrounded by municipalities with high ELI values) allowed us to identify a zone characterized by a statistically significant high density of centenarians, represented in blue color in fig1 and from now on called "Blue Zone " (BZ). BZ can be further subdivided int. a restricted zone (hereon indicated as "Restricted Blue Zone" or RBZ) ~~and a larger zone (hereon indicated as "Extended Blue Zone" or EBZ)~~ (Fig.1).

In the BZ the observed number of centenarians is quite high, i.e. 631 centenarians (269 male and 362 female centenarians) over a population of about 430.000 inhabitants. This number is about 50% higher than the expected one based on the Sardinian average and the so-called **BZ**, while representing only ¼ of the Sardinian population contains more than a half of the total number of the centenarians. Within RBZ the number of centenarians is three time higher than the expected number, and this zone appears to be really exceptional as it includes **91** centenarians **and an equal number of male (n. 47) and female (n. 44) centenarians** for a population of less than 50.000 inhabitants.

Major characteristics of the Blue Zone

Major characteristics of BZ and RBZ, in comparison to non BZ and total Sardinia are presented in Table 2. Mortality patterns in BZ and non Blue zone are clearly different and calculated life expectancies show significant differences in favour of males within the BZ. Mortality levels in the non Blue Zone are similar to other provinces in Italy while all figures are higher in the BZ especially for men The sex ratio is 1,35 in the BZ compared to 2,43 in the rest of Sardinia while there are more male centenarians compared to female centenarians in the RBZ (47 males and 44 females among the birth cohorts 1880 – 1900).

We can hypothesise that BZ has several candidate characteristics contributing to longevity at the population level. It is a mountainous region which was quite remote and difficult to reach until few decades ago. Such a geographic situation discouraged immigration, favoured inbreeding, intermarriage and consanguinity, thus decreasing the variability of the genetic pool. Moreover, agricultural economy and *pastorizia* livestock-breeding continued as important source of living until recently.The inhabitants of this area maintain the cultural and anthropological characteristics typical of the ancient traditions which are favoured by local authorities. Accordingly, nutrition and other lifestyle habits are rather conserved and healthy.

Theoretical model of non random geographical distribution of Sardinian centenarians : results of a smoothing method based on gaussian neighbourhood

The approach used to identify the BZ had an intrinsic limitation related to the discrete geographical basic units, i.e. the municipalities, and their small size. Thus, in order to obtain a general model capable of overcoming such limitations a spatial aggregation method was used. Indeed, being in Sardinia the average probability of **0.00219** centenarians per births, the requested minimal number of births, in order to find statistically significant results should be **2817** births per **basic area (defined as sum of contiguous municipalities).** Thus, only areas with chi(2) value higher than **3.841** were considered. Only 37 communes satisfied this first condition, but none of them fulfilled the minimum amount of 2817 births in order to reach on a significant chi(2) test difference. Thus, to attain this minimum required number, we used the sum of contiguous communes and, for each municipality, the shorter aggregation distance in a gaussian smoothing methodology that will ensure more than 2817 births within the considered aggregation in order to fulfil the chi-square criteria.
The main advantage of this Gaussian smoothing method was the possibility to control the degree of generalisation of the spatial distribution with a scale parameter,

and to define an optimal scale of gaussian neighbourhood in order to obtain sufficient population for statistical tests without losing to much information on geographical variability of the target phenomena. After several trials, we obtained an optimal solution by using a 15 km gaussian smoothing which is large enough, according to the average size of commune, to avoid most errors due to intra-municipal localisation of centenarians and ensuring at the same time that the size of population located in the neighbourhood is always sufficient (i.e. higher than 3000) to produce reliable tests.

The results presented on figure 1[iv] provide two different information:

(1) The intensity of the phenomena of extreme is represented on a colour scale from light yellow to deep blue. We can observe that the main area of high longevity is located in central-eastern part of the island (SE from Nuoro) but that another small peak of longevity can be observed in extreme north of the island.
(2) The probability value derived by the chi-square test of the deviation between observed and expected number of centenarians in the neighbourhood of each point is represented by red lines of various sizes according to the level of confidence significance threshold. As it takes into account the size of the sample of population, some corrections are made and we can observe that only the area located SE from Nuoro is characterised by significant positive deviations of the number of centenarians for the usual statistical thresholds of 5% or 1%.

Conclusions

The results of this approach suggest that extreme longevity can occur according to two different modalities. The first modality occurs in a defined area of high aggregation of centenarians, suggesting the presence of shared determinants favouring extreme longevity at the population level. It is a non sporadic longevity which implies a common genetic background and common environmental determinants all related to spatial consistency. The second modality of extreme longevity is more spatially dispersed, suggesting that a variety of heterogeneous determinants capable to increase the chance to reach extreme longevity at individual level. Until further investigations will be carried out it should be seen as a sporadic or random longevity that should be related to mixed individual and contextual variables.

Table 1. Comparative figures on centenarian prevalence and sex ratio

Countries and regions	**Date**	**Prevalence** (number of living centenarians per 100.000 inhabitants)	**Sex ratio** among living centenarians females/males
Belgium	**January 1st 2002**	**10.5**	**7.08**
Denmark	**July 1st 2002**	**10.4**	**6.27**
Sweden	**January 1st 2003**	**12.6**	**5.64**
Japan	**September 1st 2001**	**12.3**	**5.09**
Italy	**January 1st 2001**	**14.1**	**3.80**

Table 2. Compared characteristics of the *Restricted Blue Zone*, the *Blue Zone* and the non Blue Zone and the whole Sardinia*

VARIABLES	RESTRICTED BLUE ZONE	BLUE ZONE (including restricted BZ)	NON BLUE ZONE	TOTAL SARDINIA
Population 2001	42.113	432.475	1.199.405	1.631.880
Area (sq km)	1559	13053	11038	24090
Population density 2001	27,0	33,4	107,7	67,7
Number of communes	15	188	189	377
Average altitude	588	417	142	280
Births 1880-1900	17.865	239.439	276.837	*516.276*
Centenarians 1880-1900	91	631	501	1132
Extreme longevity index (ELI)	509	264	181	219
Male centenarians 1880-1900	47	269	146	415
Female centenarians 1880 - 1900	44	362	355	717
Male longevity index	512	218	103	156
Female longevity index	506	311	264	286
Sex ratio for centenarians 1880 - 1900	0,936	1,346	2,432	1,728
Male life expectancy at birth (1982-1998) **	75,0	74,3	73,9	74,0
Male life expectancy at 60 (1982-1998) **	20,9	20,3	19,3	19,4
Male life expectancy at 80 (1982-1998) **	8,7	8,2	7,3	7,5
Female life expectancy at birth (1982-1998) **	82,2	80,7	80,5	80,5
Female life expectancy at 60 (1982-1998) **	25,9	23,7	23,3	23,4
Female life expectancy at 80 (1982-1998) **	11,1	8,7	8,3	8,3
Population variation 1961 - 2011	-9,4%	-11,0%	28,5%	15,0%
Average size of household	3,12	3,02	3,19	3,14
Average number of rooms per housing	6,05	6,24	5,80	5,93
Work or study in commune (p 100)	37,5%	40,2%	41,0%	40,7%
Hospital beds per 10.000 inhabitants	0	43,0	68,4	61,5
TV per 100 inhabitants	23,0%	26,0%	25,3%	25,5%
Telephone per 100 inhabitants	25,5%	28,7%	30,6%	30,1%
Car per 100 inhabitants	36,6%	39,5%	46,4%	44,5%

* Data are based on our own calculations or by agregating ISTAT data at municipality level.

** Life expectancy calculated by Graziella CASELLI and Rosa Maria LIPSI based on ISTAT data (Dipartimento di Scienze Demografische, Universita La Sapienza, Roma, Italy).

Bibliography

Caselli G. and Lipsi R., 2003, *Geographical mortality differences and trends for the elderly in Sardina, 1982-1998***,** Dipartimento di Scienze Demografische, Roma.

Deiana L., Ferrucci L., Pes G.M., Carru C., Delitala G., Ganau, A., Mariotti S., Nieddu A., Pettinato S., Putzu P., Franceschi C. and Baggio G., 1999, "AKEntAnnos. The Sardinian Study of Extreme Longevity", ***Aging Clinical and Experimental Research***, 11, pp. 142-149.

Grasland C., Mathian H., Vincent J.M., 2000, "Multiscalar Analysis of discrete social phenomena : Statistical problems and political consequences", ***Statistical Journal of the United Nations ECE***, *17*, IOS Press, 157-188.

Koenig R., 2001, "Sardinia's Mysterious Male Methuselahs", ***Science***, 291, 16 March 2001, pp. 2074-2076

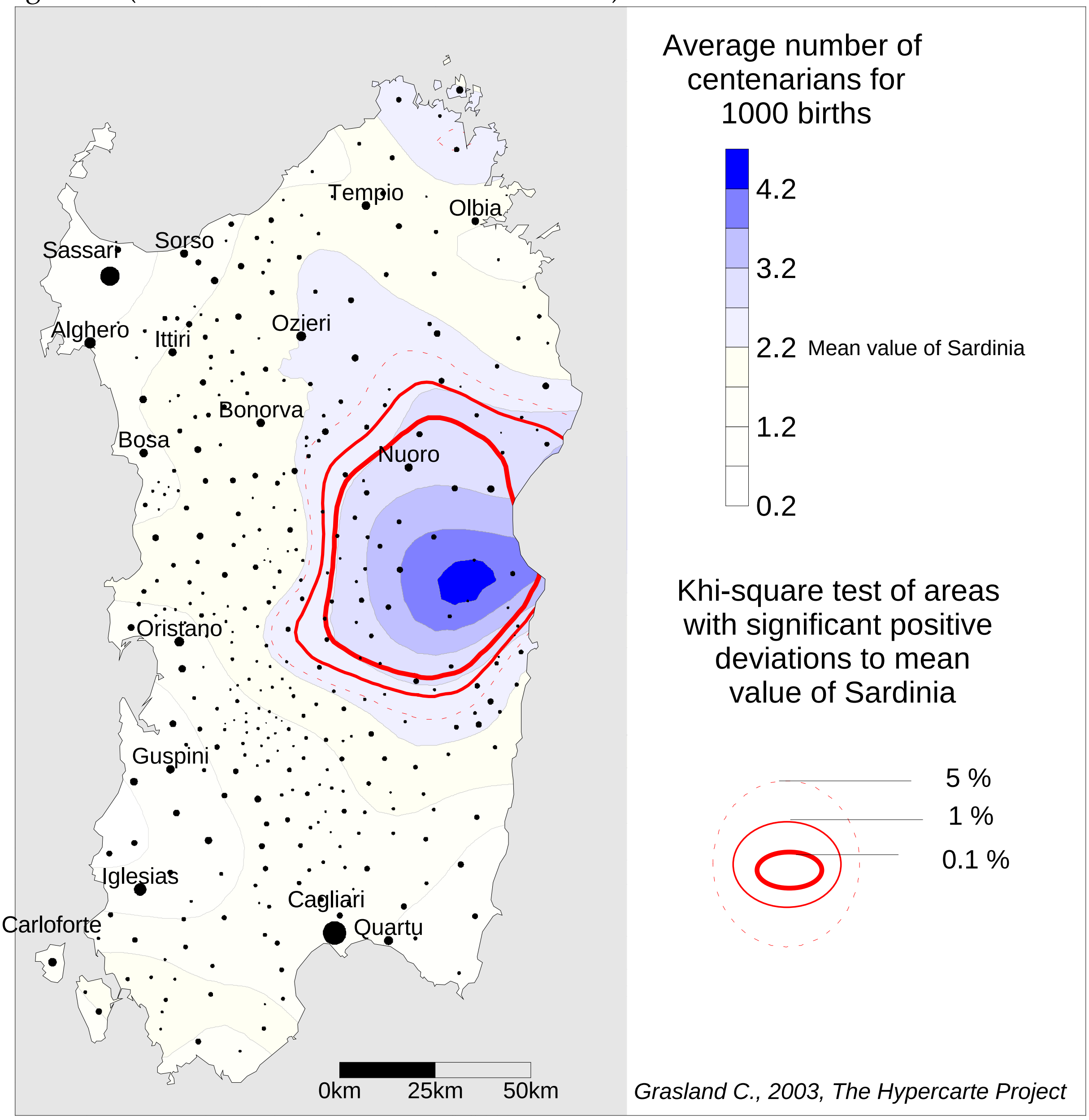
Jeune B. and Vaupel J. (editors), 1995, ***Exceptional Longevity : From Prehistory to the Present***, Odense Monographs on Population Aging 2, Odense University Press.

Jeune B. and Vaupel J. (editors), 1999, ***Validation of Exceptional Longevity***, Odense Monographs on Population Aging, 6, 249 p.

Poulain M., Pes G.M., Carru C., Baggio G., Franceschi C., Ferrucci L. and Deiana L., 2000, ***The Validation of a Population of Expectional Longevity in Sardinia***, Paper presented at the IUSSP seminar on longevity held in Montpellier in 2000 (to be published).

Note: I propose to simplify Table 1 eliminating the additional lines for Japan and Italy. If we don't, the exceptionality of the result in the Sardinia population is not very strong. Furthermore, 95%Ci for the sex ratio should be reported in an additional column (it should be easy to calculated from the original papers because is the variance for a binomial distribution). Also, specific references should be added.

Figure 1 : (Corrected version with Prob=0.00219)



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[i] We are thankful to Mrs. TOSI, Istat, Cagliari for providing us the needed data.

[ii] Please note that some changes have occurred in the delimitation of municipality territory and moreover new municipalities were created as there were only 366 at the end of the XIX[th] century.
[iii] We are collecting data on an exhaustive basis in the 214 municipalities that are place of death or place of residence of centenarians. However for these visited municipalities and despite of existence of marginal notes in birth registers the identification of all new-borns becoming centenarian somewhere else is not fully exhaustive as other centenarians may be alive or died in non-visited municipalities or outside Sardinia.

[iv] For a given point i (not necessarily a municipality centre) the gaussian smoothing method is based on the following formulas where δ is the smoothing distance :

Observed potential for centenarians observed in a gaussian surrounding with distance δ

$$\mathbf{X(i,\delta) = \Sigma_j X_j \cdot \exp(\alpha . D_{ij}^2) \quad \text{with } \alpha = \ln(0.5) / \delta^2}$$

Observed potential for births observed in a gaussian surrounding with distance δ

$$\mathbf{P(i,\delta) = \Sigma_j P_j \cdot \exp(\alpha . D_{ij}^2) \quad \text{avec } \alpha = \ln(0.5) / \delta^2}$$

Theretical potential for centenarians observed in a gaussian surrounding with distance δ

$$\mathbf{X^*(i,\delta) = P(i,\delta) * X_{tot}/P_{tot}}$$

Average potential for centenarians observed in a gaussian surrounding with distance δ

$$\mathbf{ELI(i,\delta) = X(i,\delta) / P(i,\delta)}$$

Chi-2 distance between observed and theoretical potential for centenarians in a gaussian surrounding with distance δ

$$\mathbf{Chi2(i,\delta) = [X^*(i,\delta) - X(i,\delta)]^2 / X^*(i,\delta)}$$